

**REMARKS**

**I. Status Summary**

Claims 1-27 and 46-53 are pending in the present U.S. patent application.

The specification has been objected to for the presence of embedded hyperlinks and/or other form of browser executable code on pages 27 and 30. The specification has been amended to remove the embedded hyperlinks and/or other form of browser executable code.

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5231-5236 (hereinafter "Diehl"). Claims 1-4 have also been rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy").

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans").

Claims 1, 2, 11-18, 46, and 47 have been amended. Support for the amendments can be found throughout the specification as filed, including *inter alia* in the original claims. Additional support can be found in the specification as filed at page 14 (definitions of "mapping" and "polymorphism") and page 21 (preferred method for genetic mapping is linkage analysis, whereby a phenotype is correlated with one or more detectable polymorphisms). Further support can be found in the specification as filed at page 18, lines 14-19 and in Figure 1 (crossing RI lines).

New claims 60-72 have been added. Support for the new claims can be found throughout the specification as filed, including *inter alia* in the original claims, including particularly claims 1, 2, 15-18, and 21-27. Additional support can be found in the specification as filed, including *inter alia* at page 18, lines 9-13, wherein an individual is defined to include an animal, preferably a mammal. Accordingly, no new matter has been added as a result of the claim amendments or the addition of the new claims.

Reconsideration of the application based on the remarks set forth below is respectfully requested.

II. Objection to the Specification

The specification has been objected to for the presence of embedded hyperlinks and/or other form of browser executable code on pages 27 and 30. The objection relates to the presence of two URLs on these pages. The specification has been amended to remove the embedded hyperlinks, and to include descriptive references to the websites to which the hyperlinks referred. Thus, no new matter has been added as a result of the amendments to the specification.

As a result of the amendments to the specification, applicants respectfully submit that the objection has been addressed, and respectfully request that the objection be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 102(b)

III.A. The Rejection Over Diehl

Claims 1-10, 15, 19-27, and 46-53 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl *et al.* (1997) Proc. Natl. Acad. Sci. USA 94:5231-5236 (hereinafter "Diehl"). The United States Patent and Trademark Office (hereinafter the "Patent Office") asserts that Diehl teaches a method for identifying multiple genetic loci (Col2a1, Col1a1, and Col3a1) that modulate a phenotype (facial clefting) in mice. According to the Patent Office, Diehl "performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse" using recombinant inbred (RI) mouse strains provided by M. Nesbitt. Official Action, page 3. The AXB and BXA RI lines are asserted to be crosses between A/J and C57BL6/J strains which were bred by intercrossing RI lines and maintained as a "renewable population of genetically diverse individuals". Diehl is also asserted to disclose the identification of loci using inbred lines using less than about 100 strains, identifying multiple genetic loci that modulate a phenotype, the modulation of a phenotype by a non-genetic factor (drug exposure), and the identification of an interaction among two or more non-genetic factors and a genetic locus.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Upon careful consideration of Diehl, applicants respectfully submit that Diehl does not disclose each and every element of independent claims 1 and 46. Specifically, Diehl does not disclose the renewable population of genetically diverse individuals of claims 1 and 46. According to claims 1 and 46, the renewable population of genetically diverse individuals is a population wherein a plurality of the genetically diverse individuals are heterozygous for a detectable polymorphism. Applicants respectfully submit that Diehl discloses standard recombinant inbred strains, which one of ordinary skill in the art understands to be strains of mice that are homozygous at every locus (*i.e.* not genetically polymorphic).

The Patent Office also notes that page 5231 of Diehl discloses the creation of a congenic strain by backcrossing the inbred strain A/WySn with respect to claim 2. It appears that the Patent Office is asserting that this disclosure anticipates claim 2, and applicants assume that the Patent Office is asserting this disclosure against the element of claim 2 that recites that a renewable population of genetically diverse individuals can comprise "individuals produced by backcrossing recombinant inbred lines". Applicants wish to point out, however, that this disclosure does not support a rejection under § 102 because the A/WySn strain is not a recombinant inbred strain. Rather, the A/WySn strain is a substrain of the A strain of mice, and thus is properly considered a non-recombinant inbred strain. Accordingly, even assuming *arguendo* that Diehl discloses backcrossing A/WySn mice to create a congenic strain, this disclosure does not teach backcrossing a recombinant inbred strain as recited in claim 1 to genetically map a locus associated with a phenotype. As indicated in the specification of the instant application (see page 12, lines 20-23), a congenic line is a recombinant inbred line, but applicants respectfully submit that the strain used to create the congenic line in Diehl (*i.e.* A/WySn) is not a recombinant inbred line. As a result, applicants respectfully submit that Diehl does not anticipate this element of amended claim 1.

As such, applicants respectfully submit that claims 1 and 46 have been patentably distinguished over Diehl. Claims 2-10, 15, 19-27, and 47-53 all depend directly or indirectly from claim 1 or from claim 46, and thus are also believed to be distinguished from Diehl. Accordingly, applicants respectfully request that the rejection of claims 1-10, 15, 19-27, and 46-53 based on Diehl be withdrawn. Allowance of these claims is also respectfully requested.

### III.B. The Rejection Over Bellamy

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bellamy *et al.* (1991) *Human Genetics* 87:341-347 (hereinafter "Bellamy"). According to the Patent Office, Bellamy teaches a method for identifying a genetic locus that modulates a phenotype comprising (a) providing a renewable population of diploid humans that are genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Further, Bellamy is asserted to teach the above method wherein the renewable population comprises a panel of cell lines derived from the genetically diverse individuals.

After considering the rejection and the Patent Office's basis for the rejection, applicants respectfully traverse the rejection and submit the following.

Initially, applicants respectfully submit that the Patent Office is overstating the teachings of Bellamy. More specifically, applicants respectfully submit that Bellamy does not disclose mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype and identifying a genetic locus that modulates the phenotype through the mapping step. Close inspection of Bellamy reveals that the reference only discloses a visual comparison of band sharing among DNA fingerprints from members of two populations leading to the observation that band sharing occurs more frequently in an inbred population than would be expected if the population were not inbred.

Stated another way, the authors used multilocus probes to investigate whether band sharing in an inbred population was higher than that seen in an outbred

population. Applicants respectfully submit that this method is not a mapping method, and thus does not support an anticipation rejection of the method of claim 1, which specifically recites mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, and identifying a genetic locus that modulates the phenotype. As the reference does not teach a mapping step and an identifying step whereby a genetic locus that modulates a phenotype is identified, applicants respectfully submit that the reference does not anticipate claim 1.

Additionally, the Patent Office asserts that “the phenotype that is modulated is the increased band sharing as evidenced by using four different multi-locus probes”. See Official Action at page 7. Applicants respectfully submit that increased band sharing is not a phenotype as that term is understood by one of ordinary skill in the art or as it is used in the instant application. According to the specification as filed, “the term ‘phenotype’ or ‘trait’ each refers to any observable property of an organism, produced by the interaction of the genotype of the organism and the environment”. Applicants respectfully submit that band sharing (a) is not “an observable property of an organism (at best it is an observable property of a population), and (b) does not arise from an interaction of the organism’s genome with the environment. As such, a phenotype is something that is a characteristic of an individual, and does not require reference to the rest of the population. Thus, applicants respectfully submit that band sharing is not a “phenotype” as that term is used in the instant application and is understood by the skilled artisan. Furthermore, applicants respectfully submit that band sharing is a fixed property describing the genetic material of the organism, and as such is a genotype, not a phenotype.

Moreover, even assuming *arguendo* that band sharing is a “phenotype” in some sense of the term, applicants respectfully submit that the Patent Office is incorrect in stating that increased band sharing is modulated by a genetic locus. Rather, the increased band sharing is a passive consequence of the fact that the population in question is an inbred population. Therefore, applicants respectfully submit that the increased band sharing that was observed is wholly dependent on the artificially low degree of genetic diversity in the inbred population versus an outbred population, which

is not properly considered. Stated another way, since inbreeding results in certain bands becoming “fixed” in the inbred gene pool, Bellamy does no more than show that the presence of this phenomenon in the population in question indicates that the population is an inbred population.

Claim 1, on the other hand, recites identifying a genetic locus that modulates the phenotype. Applicants respectfully submit that the “phenotype” disclosed in Bellamy (assuming that it is a “phenotype” at all) is not modulated by any genetic locus. Rather, the “phenotype” is simply an observation across a population that arises by simple breeding within this relatively closed population. Thus, the disclosure of Bellamy cannot be deemed to teach identifying a modifying genetic locus because Bellamy does not involve a situation where any genetic loci are acting to increase or decrease the occurrence of the “phenotype”.

Accordingly, applicants respectfully submit that claim 1 has been patentably distinguished over Bellamy. Claims 2-4 depend from claim 1, and thus are believed also to have been patentably distinguished over Bellamy. As a result, applicants respectfully request that the rejection of claims 1-4 over Bellamy be withdrawn.

#### IV. Claim Rejection Under 35 U.S.C. § 103

Claims 11-14 and 16-18 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans *et al.* (1986) J. Immunol 137:2355-2360 (hereinafter “Dindzans”), and further in view of Hedrich (1981) Genetic Monitoring, Chapter 8 in The Mouse in Biomedical Research, volume I (hereinafter “Hedrich”). The bases for these rejections can be found in the Official Action at pages 7-11. The Patent Office asserts that Diehl teaches a method for identifying multiple genetic loci. The Patent Office concedes, however, that Diehl does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines.

The Patent Office asserts that Dindzans teaches multiple parents are necessary for breeding of mice in an attempt to map genes and in the elucidation of mechanisms of genetic control. The Patent Office concedes, however, that Dindzans does not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines. The

Patent Office asserts that this deficiency is cured by Hedrich, which is asserted to teach the organization of breeding colonies from a founding colony made up of 8-10 breeding pairs. The Patent Office thus contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype of Diehl so as to have included the diverse population of non-recombinant, parent lines derived from at least 3, 4, or 8 non-recombinant parent lines.

After carefully considering the rejection and the Patent Office's asserted bases in support of the rejection, applicants respectfully traverse the rejection and offer the following remarks.

Claims 11-14 and 16-18 all depend directly or indirectly from claim 2. Based on its dependency from claim 1, claim 2 recites *inter alia* a method for identifying a genetic locus that modulates a phenotype comprising

- (a) providing a renewable population of genetically diverse individuals, wherein a plurality of the genetically diverse individuals are heterozygous for a detectable polymorphism, wherein the renewable population of genetically diverse individuals comprises:
  - (i) individuals produced by crossing recombinant inbred lines;
  - (ii) individuals produced by backcrossing recombinant inbred lines;
  - (iii) a cloned population of genetically diverse individuals; or
  - (iv) a panel of cell lines derived from genetically diverse individuals;
- (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype; and
- (c) identifying a genetic locus that modulates the phenotype through the mapping step.

Claims 11-14 and 16-18 then recite that the recombinant inbred lines comprise recombinant inbred lines derived from at least 3 (claims 11 and 16), 4 (claims 12 and 17), or 8 (claims 13 and 18) non-recombinant parent lines. Claim 14 depends from claim 11, and recites that at least one of the at least three different non-recombinant

parent lines is selected from the group consisting of mouse lines C57BL/6, BALB/c, C3H, A, 129, and DBA/2.

Applicants respectfully submit that the cited references, alone or in combination, do not support a *prima facie* case of obviousness because the cited references do not disclose or suggest all of the elements of claim 2, each of which is also an element of claims 11-14 and 16-18.

The above-noted deficiencies of the Diehl reference are incorporated here by reference. Applicants respectfully submit that neither Dindzans nor Hedrich, alone or in combination, cures the deficiencies of Diehl vis-à-vis claim 1 (and by dependency, claim 2). Stated another way, Diehl does not teach “providing a renewable population of genetically diverse individuals, wherein a plurality of the genetically diverse individuals are heterozygous for a detectable polymorphism.”

Neither Dindzans nor Hedrich, alone or in combination, teach or suggest this element of claim 2. Applicants respectfully submit that since claim 2 has been patentably distinguished over the combination of references, claims 11-14 and 16-18 have been patentably distinguished over these references based upon their dependency from claim 2. Accordingly, applicants respectfully submit that a *prima facie* case of obviousness has not been made out, and further respectfully request that the rejection of claims 11-14 and 16-18 over Diehl, Dindzans, and Hedrich be withdrawn at this time.

Moreover, applicants respectfully submit that the Patent Office is inaccurately summarizing the teachings of Dindzans. In response to statements presented by Applicants in the previous Amendment (Amendment B, dated December 5, 2003), the Patent Office asserts the following:

Dindzans was relied upon for its teachings of non-recombinant parental lines in its teaching of “the AXB/BXA RI strains used in these experiments were derived from susceptible (C57BL/6J) and resistant (A/J) progenitors representing extremes in disease” for the sole purpose of creating RI strains exhibiting distinct patterns of MHV-3 induced liver pathology. The reference thus teaches that multiple progenitors were used to establish their population for the expected benefit that using multiple progenitors creates a “unique assortment of parental genes” which is “useful for the



mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control".

Official Action, page 12. While it may be true that "multiple progenitors were used to establish their population [to create] a unique assortment of parental genes", applicants respectfully submit that these "multiple progenitors" were not derived from 3, 4, or 8 non-recombinant parents. This is clearly indicated on page 2356 of Dindzans, wherein it states "RI strains were derived by inbreeding mice from the F<sub>2</sub> generation of the cross between A/J (A) and C57BL/6J (B) mice..." (emphasis added). Thus, the only non-recombinant parental strains used in Dindzans were the A/J and C57BL/6J strains, and as a result, applicants respectfully point out that Dindzans only used 2 non-recombinant parental lines and not the at least 3 recited in claims 11-14 and 16-18 of the instant application. As such, applicants respectfully submit that Dindzans does not disclose the use of 3, 4, or 8 non-recombinant parent lines. This deficiency is conceded on page 10 of the Official Action, which states that "Dindzans et al. do not teach the derivation of the RI lines from at least 3, 4, or 8 non-recombinant parent lines".

Stated another way, applicants traverse the Patent Office's assertion that Dindzans "teaches that multiple progenitors were used to establish their population for the expected benefit that using multiple progenitors creates a 'unique assortment of parental genes' which is 'useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control'." The Patent Office appears to be confusing the use of "multiple progenitors" in the establishment of RI lines as performed by Dindzans and the use of 3, 4, or 8 non-recombinant parent lines in the establishment of the renewable population of genetically diverse individuals as recited in claim 2. Applicants reiterate that Dindzans employed only 2 non-recombinant parent lines, and that the "multiple progenitors" used to establish their RI lines can only refer to those progeny derived from breeding these two non-recombinant parent lines. These "multiple progenitors" are not non-recombinant parent lines (or members of non-recombinant parent lines), and thus are not applicable to the elements of claims 11-14 and 16-18. Rather, once the C57 and A/J mice are bred, all progeny that result (as well as all of their progeny) are recombinant (thus the term recombinant inbred strain that

attaches when these mice are inbred), having one C57 and one A/J allele at every locus.

These recombinant animals are then inbred to produce recombinant inbred strains that are homozygous for either the C57 or the A/J allele at every locus. Applicants acknowledge that multiple breeding pairs are used to create RI lines, but unless these breeding pairs can trace their genomes back to 3, 4, or 8 non-recombinant parents, this fact is immaterial to the subject matter of claims 11-14 and 16-18. Since the RI strains disclosed in Dindzans are homozygous for either the A/J allele or the C57 allele at every locus of their genomes, Dindzans does not disclose genetically diverse individuals that are heterozygous for a detectable polymorphism (or, in fact, that are heterozygous at any locus whatsoever).

Claims 11-14 and 16-18 recite *inter alia* the use of a renewable population of genetically diverse individuals, wherein the renewable population of genetically diverse individuals comprises: (i) individuals produced by crossing recombinant inbred lines; and (ii) individuals produced by backcrossing recombinant inbred lines, and the use of RI lines that are generated by crossing at least 3, 4, or 8 different non-recombinant parent lines. Diehl is conceded not to teach this element on page 9 of the Official Action. Dindzans is conceded not to teach this element on page 10 of the Official Action. Applicants respectfully submit that Hedrich does not cure these deficiencies. Accordingly, applicants respectfully reiterate that a *prima facie* case of obviousness has not been made.

According to the Patent Office, "Hedrich's teaching of 8-10 breeding pairs makes obvious the use of at least 3, 4, or 8 non-recombinant parent lines of Dindzans...". Official Action, page 12. Applicants respectfully traverse this assertion, because Dindzans does not disclose the use of 3, 4, or 8 non-recombinant parent lines. Furthermore, applicants respectfully submit that contrary to the Patent Office's assertion, Hedrich does not "make obvious the use of at least 3, 4, or 8 non-recombinant parent lines" at all. Applicants respectfully submit that Hedrich contains no more than a standard disclosure of how to breed mouse lines and set up breeding colonies. It does not disclose breeding together 3, 4, or 8 genetically unrelated

individuals (e.g. 3, 4, or 8 non-recombinant mouse lines) as part of the breeding program, particularly as part of a breeding program designed in part to produce recombinant inbred mice and their progeny.

Rather, as shown on page 171 of Hedrich, the disclosure relates to “the propagation of an inbred strain” (emphasis added). Thus, it relates to the breeding of individuals that are all from one inbred strain with the goal of creating genetically identical animals, thereby maintaining the integrity of the inbred strain (*i.e.* its homozygosity at every locus). Accordingly, applicants respectfully submit that the skilled artisan would have no motivation to combine Diehl, Dindzans, and Hedrich, all of which teach the use or creation of mice that are homozygous at every locus, to arrive at the instant invention, which involves the creation of mice that are heterozygous (*i.e.*, intentionally not homozygous at every locus), with a reasonable expectation of success since the crucial characteristic of the mice disclosed in the cited references is that each mouse is genetically identical to each other mouse of the same strain.

This is particularly true in view of the fact that Dindzans teaches that it is important to have a unique assortment of parental genes that are homozygous at every locus, as such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control” (Dindzans at page 2355), a point that is conceded by the Patent Office on page 10 of the Official Action of March 5, 2004. As such, Dindzans teaches that homozygosity at every locus is critical to the use of RI lines. To the contrary, the instant subject matter as recited in claim 2 pertains *inter alia* to crossing and backcrossing these RI lines for the express purpose of creating new animals (or cells) that are NOT homozygous at each and every locus. Thus, Dindzans, like Hedrich, teaches away from the subject matter recited in claim 2. As a result, applicants respectfully submit that one of ordinary skill in the art would not, and indeed could not, have combined the teachings of Diehl, Dindzans, and Hedrich to arrive at the invention recited in claims 11-14 and 16-18 with a reasonable expectation of success because the crosses recited in claim 2, subsections (i) and (ii), destroy the homozygosity that Dindzans teaches is critical for mapping. Therefore, even if assuming *arguendo* that the use of 3, 4, or 8 different non-recombinant parent lines is

suggested by Hedrich (which applicants respectfully submit is not the case), the creation of recombinant inbred intercross or backcross animals from 3, 4, or 8 different non-recombinant parent lines is not suggested by the combination of the cited references because the cited references teach away from the production of individuals that are not homozygous at every locus.

Summarily, applicants respectfully submit that when the disclosures of the cited references are taken in their entirety, they do not suggest the desirability of creating the renewable population of genetically diverse individuals recited in claim 2. As a result, the cited references cannot be deemed to motivate the skilled artisan to create a renewable population of genetically diverse individuals derived from breeding 3, 4, or 8 different non-recombinant parent lines as recited in claims 11-13 and 16-18 with a reasonable expectation of success. Furthermore, they cannot be deemed to suggest a renewable population of genetically diverse individuals derived from breeding 3 different non-recombinant parent lines wherein at least one of the at least three different non-recombinant parent lines is selected from the group consisting of mouse lines C57BL/6, BALB/c, C3H, A, 129, and DBA/2 as recited in claim 14.

Accordingly, applicants respectfully submit that the rejection of claims 11-14 and 16-18 over the combination of Diehl, Dindzans, and Hedrich has been addressed, and respectfully request the withdrawal of the rejection. Applicants further submit that claims 1-27 and 46-53 are in condition for allowance at this time, and respectfully solicit a Notice of Allowance to that effect.

#### **VI. Discussion of the New Claims**

New claims 60-72 have been added. Support for the new claims can be found throughout the specification as filed, including *inter alia* in the original claims. Additional support can be found on page 13, lines 14-15, page 18, lines 14-16, and on page 7, lines 5-9, of the specification as filed. Additional support can be found in the specification as filed, including *inter alia* at page 18, lines 9-13, wherein an individual is defined to include an animal, preferably a mammal.

Applicants respectfully submit that the new claims are patentably distinguishable over the combination of Diehl, Dindzans, Hedrich, and/or Bellamy for reasons similar to those given hereinabove regarding the pending rejection under 35 U.S.C. § 103(a). With respect to claims 60-63, applicants respectfully submit that the combination of references does not disclose crossing or backcrossing recombinant inbred mice, because this would destroy the homozygosity at each locus that is a hallmark of these strains, and further that there is no teaching or suggestion in the references to generate recombinant inbred lines (or recombinant inbred intercross mice) by crossing 3, 4, or 8 different non-recombinant parent lines. With respect to claims 64-72, applicants respectfully submit that the cited references do not disclose mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype and identifying a genetic locus that modulates the phenotype through the mapping step.

Because the cited references do not disclose or suggest each and every element of new claims 60-72, and further because the cited references do not provide a motivation to the skilled artisan to combine the references to arrive at the claimed invention with a reasonable expectation of success, applicants respectfully submit that new claims 60-72 have been patentably distinguished over the combination of Diehl, Dindzans, Hedrich, and/or Bellamy. Accordingly, applicants respectfully submit that claims 60-63 are also in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

### CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Serial No.: 09/998,058

DEPOSIT ACCOUNT

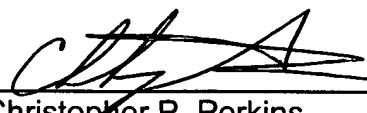
The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: July 6, 2004

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421/34/2     AAT/CP/ptw

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